The Inflammasomes in Kidney Disease

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ABSTRACT

Renal inflammation is a universal response to infectious and noninfectious triggers. Sensors of the innate immune system, such as Toll-like receptors or RIG-like receptors, provide danger recognition platforms on renal cells that integrate and translate the diverse triggers of renal inflammation by inducing cell activation and the secretion of proinflammatory cytokines and chemokines. As a new entry, the inflammasome-forming NLR genes integrate various danger signals into caspase-1-activating platforms that regulate the processing and secretion of pro-IL-1β and pro-IL-18 into the mature and active cytokines. Accumulating data now document a role for the NLRP3 inflammasome and IL-1β/IL-18 in many diseases, including atherosclerosis, diabetes, amyloidosis, malaria, crystal-related diseases, and other autoimmune disorders, identifying this innate immune pathway as an attractive therapeutic target. Here we review the current knowledge regarding inflammasome signaling and outline existing evidence on the expression and functional role of the inflammasome-caspase-1-IL-1β/IL-18 axis in kidney disease. We further provide a perspective on the potential roles of the inflammasomes in the pathogenesis of acute and chronic kidney diseases.


NLR GENES AND THE INFLAMMASOME

The NLR gene family consists of 22 members in humans, 35 in mice, and several hundreds in plants. NLR genes have conserved NACHT domains that mediate nucleotide (ATP or GTP)-dependent protein oligomerization (Figure 2). Almost all members also contain a C-terminal leucine-rich repeat domain that likely functions in ligand sensing. The NLR genes can further be subdivided...
based on the presence of CARD (caspase recruitment domain), PYD (pyrin domain), and acidic transactivation or baculovirus inhibitory N-terminal domains. As a group, the NLRs primarily activate NF-κB signaling or form caspase-activating platforms termed inflammasomes. As an example, the best characterized NLRs are NOD1 and NOD2 (NLRC1 and NLRC2, in which “NLRC” indicates a NLR containing a CARD) that activate NF-κB in response to bacterial peptidoglycans and contribute to Crohn’s disease. 

The NLRP (nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin, domain containing) subfamily includes 14 proteins that are...
defined by a conserved N-terminal PYD domain and common NACHT and leucine-rich repeat motifs (Figure 2). Upon activation, the NLRP proteins oligomerize through homotypic molecular interactions and recruit the PYD-CARD adaptor protein, ASC, and the protease caspase-1 to form a protein complex termed the inflammasome (Figure 3).12,13 Unlike the typical signaling cascades downstream of many innate receptors such as the TLRs or other NLR members such as NOD1/2, the inflammasome is a proteolytic caspase-1-activating platform. Caspase-1, an inflammatory caspase, does not play a major role in apoptosis. Instead, activated caspase-1 processes numerous cellular substrates including the cytokines IL-1β and IL-18.18,19 The generation of mature IL-1β and IL-18 involves two separate processes: the induction of NF-kB-dependent mRNA expression and translation of a procytokine (signal 1) followed by cleavage of the procytokine and release of mature and active cytokine (signal 2).13,20 Only the latter depends directly on the inflammasome (Figure 1).

In the case of IL-1β, caspase-1 cleaves the 35-kD pro-IL-1β to the mature and secreted form of the 17-kD cytokine. Other enzymes can also cleave these procytokines in caspase-1-deficient mice (e.g., caspase-4, -5; caspase-11, -12 in mice-11, and -12 in mice; chymotrypsin; chymase; granzyme; elastase; plasmin; or proteinase-3), but the functional relevance of these enzymes for IL-1β/IL-18 secretion is unclear.21,22 Caspase-1 has more than 40 other cellular substrates.18 In addition to processing cytokines, inflammasomes mediate an inflammatory form of cell death termed “pyroptosis” and may also be involved in cellular processes such as glycolysis.18,23 Pyroptosis was only recently described in macrophages and consists of programmed cell death involving loss of membrane integrity, unlike apoptosis, in association with IL-1β and IL-18 secretion.23,24

Because they were discovered fairly recently, our knowledge about the biology of the NLRP proteins and the inflammasome is somewhat limited. Unlike the other families of pattern recognition receptors that have recognizable PAMP ligands, ligands for many NLRP members or even their function are not yet known. Early studies attempted to establish the NLRP proteins and the inflammasome as sensors of microbial constituents similar to the TLR paradigm. However, more recent work identifies many diverse microbial, nonmicrobial, and even endogenous stimuli that activate the inflammasome (Table 1). These observations put into question a ligand-specific model of inflammasome activation, as is the case for the TLRs. Rather, existing evidence supports the notion that the inflammasome is the final common pathway that senses cellu-
lar stress or injury. As such, the inflammasome-caspase-1-IL-1β/IL-18 axis is involved in many disease conditions (Table 2). Therefore, it is very likely that inflammasomes are also involved in renal inflammation, either during infectious or during noninfectious types of kidney disease.

THE NLRP3 INFLAMMASOME

The best understood inflammasome is NLRP3, which is activated by various stimuli and expressed primarily in macrophages and dendritic cells. Mutations in the NLRP3 gene are linked to three autoinflammatory disorders that include Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and chronic infantile neurologic cutaneous and articular syndrome. Provided that microbial or nonmicrobial stimuli activate NF-κB to induce pro-IL-1β and IL-18 (signal 1), a diverse group of additional stimuli can act as signal 2 to activate caspase-1 through NLRP3 (Table 1). These stimuli represent additional PAMPs and DAMPs that do not match with those activating TLRs. For example, cellular necrosis triggers NLRP3 activation in macrophages by release of ATP or uric acid. The multitude of NLRP3 triggers underscores the likely function of this inflammasome as a sensor of cellular stress or injury operating through a single common pathway. For example, the activation of NLRP3 occurs after endosomal stress and the activation of lysosomal proteases such as cathepsin B. In studies that involve endosomal loading with viral or crystal aggregates such as adenovirus or silica, inhibition of endosomal maturation or lysosomal protease activity is sufficient to block inflammasome activation. A second model of activation proposes that engagement of ATP-dependent P2X7 receptors results in the opening of large pannexin-1 pores in the cell membrane (Figure 1). The open pannexin-1 pores allow NLRP3-activating bacterial PAMPs into the cytoplasm, resulting in inflammasome activation. A third model of activation proposes that engagement of ATP-dependent P2X7 receptors results in the opening of large pannexin-1 pores in the cell membrane. The opening of these pores is sufficient to trigger inflammasome activation. Finally, a recent paper by Zhou and colleagues suggests the final
The common pathway of NLRP3 inflammasome activation is through oxidative stress and thioredoxin-interacting protein (TXNIP). In the normal state, TXNIP is bound to the antioxidant reductase, thioredoxin. After oxidative stress, TXNIP releases from thioredoxin to interact with and activate NLRP3. Because many NLRP3-activating stimuli are associated with ROS production, this represents a potential unifying model.

In addition to these models, several other signaling molecules and cellular events are essential for NLRP3 inflammasome activation. K+ efflux from the cell is necessary for activation of the NLRP3 inflammasome regardless of the stimulus.27 In response to certain infectious agents such as Candida albicans or malarial hemoglobin, the tyrosine kinases spleen tyrosine kinase and Lyn are also essential for optimal activation of the NLRP3 inflammasome.32,36 CARD9, phosphoinositide 3-kinase, and extracellular signal-regulated kinase signaling downstream of spleen tyrosine kinase appears necessary not only to induce expression of pro-IL-1β but also to exert a direct effect on ASC and caspase-1 after exposure to these pathogens. Finally, recent studies show that cellular priming is required not only to transcribe and translate inflammasome substrates such as IL-1β and IL-18, but also to induce the expression of NLRP3 required for inflammasome assembly and activation.37

### OTHER INFLAMMASOMES

Other proteins that are known to form inflammasomes include the NLRs, NLRP1, NLRC4 (Ipaf-1), and the human interferon-inducible 200 protein AIM2 (absent in melanoma-2) (Figure 2).32 NLRC4 responds to bacterial flagellin and bacteria containing type III/IV secretion systems such as Salmonella typhimurium and Pseudomonas aeruginosa.38 NLRC4 can activate caspase-1 through a direct CARD-CARD interaction in the absence of the adaptor, ASC.39,40 NLRP1 inflammasome is activated by Bacillus anthracis lethal toxin and the peptidoglycan muramyl dipeptide (Table 1).41 Finally, AIM2 is a PYD containing human interferon-inducible 200 protein that does not belong to the NLR family. AIM2 forms a DNA-sensing inflammasome with ASC and caspase-1 that mediates cytokine processing and pyroptosis.42–45 In contrast to NLRP3, AIM2 acts as a receptor that is activated by DNA binding. AIM2 is involved in antiviral host defense and the response to Listeria monocytogenes and Francisella tularensis.46–49 The identification of AIM2 is also significant for demonstrating that ASC- and caspase-1-containing inflammasomes are not restricted to the NLR family of genes. The role of these inflammasomes in nonmicrobial inflammation and kidney disease is unknown. Other NLRs such as NLRP2 and NLRP12 have also been shown to interact with ASC and activate caspase-1 in vitro; however, the biologic significance of these observations and whether these NLRs form true inflammasomes is unclear.50,51

### DISEASE ENTITIES INVOLVING THE INFLAMMASOME-CASPASE-1-IL-1B/IL-18 AXIS

Several human autoinflammatory syndromes are directly related to variations in inflammasome or IL-1-related genes (Table 2). The cryopyrin-associated periodic syndromes encompass Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and chronic infantile neurologic cutaneous and ar-
ticular syndrome and are all caused by different gain-of-function mutations in the NLRP3 gene. The deficiency of IL-1 receptor (IL-1R) antagonist syndrome is also associated with increased circulating IL-1 levels. Although none of these diseases is known to directly affect the kidney, a role for NLRP3 or IL-1 signaling in renal pathology cannot be excluded.

The pathogenic role of IL-1 in all of the aforementioned diseases was clearly documented by complete remissions of their related symptoms upon therapy with IL-1 antagonists. IL-1 blockade is also partially therapeutic in several other hereditary or idiopathic autoinflammatory diseases, but the precise mechanisms of direct or indirect involvement of inflammasomes is yet unclear (Table 2). Crystal-induced pathologies form another group of diseases that are recently related to NLRP3-mediated IL-1/IL-18 secretion. Monosodium urate or calcium pyrophosphate dihydrate crystals activate the NLRP3 inflammasome, which is now thought to represent a central pathogenic mechanism of gout and pseudogout. IL-1 antagonism immediately ameliorates the clinical symptoms of these crystal arthropathies. In vitro studies and studies performed in mice also support a role of the NLRP3 inflammasome in translating the recognition of crystal or particle formats of silica, asbestos, cholesterol, β-amyloid, or hemozoin into IL-1β release and disease manifestations of silicosis, asbestosis, atherosclerosis, Alzheimer’s disease, and multiple sclerosis.

Table 2. Noninfectious diseases recently related to inflammasomes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Potential Mechanism</th>
<th>IL-1 Blockade</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF</td>
<td>GOF mutation in the pyrin gene</td>
<td>CR</td>
<td>95, 96</td>
</tr>
<tr>
<td>PAPA</td>
<td>GOF mutation in the PSTPIP1 gene</td>
<td>CR</td>
<td>97, 98</td>
</tr>
<tr>
<td>FCAS</td>
<td>GOF mutation in the NLRP3 gene</td>
<td>CR</td>
<td>53, 99</td>
</tr>
<tr>
<td>MWS</td>
<td>GOF mutation in the NLRP3 gene</td>
<td>CR</td>
<td>21, 53</td>
</tr>
<tr>
<td>CINCA</td>
<td>GOF mutation in the NLRP3 gene</td>
<td>CR</td>
<td>99</td>
</tr>
<tr>
<td>DIRA</td>
<td>LOF mutation in the IL-1Ra gene</td>
<td>CR</td>
<td>55</td>
</tr>
<tr>
<td>HIDS</td>
<td>Mevalonate kinase deficiency, ?</td>
<td>PR/CR</td>
<td>100</td>
</tr>
<tr>
<td>TRAPS</td>
<td>GOF mutation in the TNF-R1 gene</td>
<td>PR/CR</td>
<td>101</td>
</tr>
<tr>
<td>FCAS2</td>
<td>GOF mutation in the NLRP12 gene</td>
<td>?</td>
<td>102</td>
</tr>
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</table>

Idiopathic syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Potential Mechanism</th>
<th>IL-1 Blockade</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>adult-onset Still syndrome</td>
<td>?</td>
<td>PR/CR</td>
<td>103</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>?</td>
<td>PR/CR</td>
<td>104</td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
<td>?</td>
<td>PR</td>
<td>103</td>
</tr>
<tr>
<td>ankylosing spondylitis</td>
<td>?</td>
<td>PR</td>
<td>99</td>
</tr>
<tr>
<td>polychondritis</td>
<td>?</td>
<td>PR/CR</td>
<td>105</td>
</tr>
<tr>
<td>Schnitzler’s syndrome</td>
<td>?</td>
<td>CR</td>
<td>106</td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td>?</td>
<td>CR</td>
<td>107</td>
</tr>
<tr>
<td>anti-synthetase syndrome</td>
<td>?</td>
<td>PR/CR</td>
<td>108</td>
</tr>
<tr>
<td>SLE</td>
<td>Self DNA activating AIM2?</td>
<td>PR</td>
<td>109</td>
</tr>
<tr>
<td>gout/pseudogout</td>
<td>Crystal-induced NLRP3 activation</td>
<td>CR</td>
<td>56</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Amyloid-β-induced NLRP3 activation</td>
<td>?</td>
<td>61</td>
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<tr>
<td>amyloidosis</td>
<td>Amyloid-β-induced NLRP3 activation</td>
<td>?</td>
<td>61</td>
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<tr>
<td>atherosclerosis</td>
<td>Lipid crystal-induced NLRP3 activation</td>
<td>?</td>
<td>60</td>
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<tr>
<td>diabetes</td>
<td>Glucose-induced NLRP3 activation</td>
<td>PR</td>
<td>35</td>
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<tr>
<td>arterial hypertension</td>
<td>GOF mutation in the NLRP3 gene</td>
<td>?</td>
<td>110</td>
</tr>
<tr>
<td>heart failure after myocardial infarction</td>
<td>ROS-induced NLRP3 activation</td>
<td>PR</td>
<td>111</td>
</tr>
<tr>
<td>stroke</td>
<td>ROS-induced NLRP3 activation</td>
<td>PR</td>
<td>112</td>
</tr>
<tr>
<td>CNS trauma</td>
<td>?</td>
<td>PR</td>
<td>113</td>
</tr>
<tr>
<td>multiple sclerosis</td>
<td>?</td>
<td>PR</td>
<td>114</td>
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Environmental diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Potential Mechanism</th>
<th>IL-1 Blockade</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>asbestosis</td>
<td>Particle-induced NLRP3 activation</td>
<td>?</td>
<td>59</td>
</tr>
<tr>
<td>silicosis</td>
<td>Particle-induced NLRP3 activation</td>
<td>?</td>
<td>29</td>
</tr>
<tr>
<td>malaria</td>
<td>Hemozoin-induced NLRP3 activation</td>
<td>?</td>
<td>62</td>
</tr>
<tr>
<td>sunburn</td>
<td>UV-B light-induced NLRP3 activation</td>
<td>?</td>
<td>115, 116</td>
</tr>
<tr>
<td>toxic skin disease</td>
<td>Irritant-induced NLRP3 activation</td>
<td>?</td>
<td>93</td>
</tr>
<tr>
<td>toxic liver injury</td>
<td>?</td>
<td>?</td>
<td>117</td>
</tr>
<tr>
<td>toxic colon injury</td>
<td>?</td>
<td>?</td>
<td>118, 119</td>
</tr>
</tbody>
</table>

FMF, familial Mediterranean fever; GOF, gain-of-function; CR, complete remission; PR, partial remission; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; CINCA, chronic infantile neurological cutaneous and articular syndrome; DIRA, deficiency in IL-1R antagonist; LOF, loss-of-function mutation; HIDS, hyper IgD syndrome and mevalonic aciduria; TRAPS, TNF receptor-associated periodic syndrome; ROS, reactive oxygen species; COPD, chronic obstructive pulmonary disease; UV, ultraviolet.
malaria.32,62 It would be interesting to know whether the same mechanism applies to kidney diseases that are associated with crystals or microparticles such as nephrolithiasis, renal amyloidosis, cholesterol embolism, urate nephropathy, cast nephropathy, or rhabdomyolysis. Production of reactive oxygen species is another stimulus for NLRP3 activation. Interestingly, IL-1 blockade also improves diabetes by increasing insulin secretion, most likely by promoting β cell survival.64

Together, beyond signaling infection, inflammasome-mediated IL-1β/IL-18 secretion is involved in several different noninfectious diseases, suggesting that inflammasomes generally convey cell stress to the immune system.

RENA L NLR GENE EXPRESSION

Little is known of the expression of inflammasome-related genes in renal cells or in kidney diseases. Figure 4 illustrates mRNA expression profiles of NLR genes in human and mouse solid organs, including the kidney.65 It should be noted that except for NLRP2 and NLRP10, the human kidney expresses much lower mRNA levels of most inflammasome-related molecules as compared with the human spleen. In contrast, kidneys from 6-week-old C57BL/6 mice express much higher levels of most NLR genes compared with the spleen, with the exception of neuronal apoptosis inhibitory protein and NLRP3 (Figure 4). Although these data illustrate species-specific differences in inflammasome expression under healthy conditions, it is well known that inflammasome-related genes can be strongly induced by proinflammatory cytokines or TLR agonists.12 Which cells express functional inflammasomes in the kidney is largely unknown. Several studies document the potential of tubular epithelial cells to secrete IL-1β and IL-1866; hence, they should harbor all necessary elements of the inflammasome-caspase-1-IL-1β/IL-18 axis.

Figure 4. mRNA expression of inflammasome-related molecules in solid organs of humans and mice. The left panel illustrates quantitative real-time PCR performed on prenormalized cDNAs derived from poly(A)-selected DNase-treated RNAs purified from pools of healthy human tissues. The right panel illustrates respective data from cDNAs of adult C57BL/6 mice. All expression data were normalized to the respective glyceraldehydes 3-phosphate dehydrogenase (GADPH) mRNA level. Spleen mRNA expression levels are shown on top of the table. The table displays relative expression levels to the respective expression level of each transcript in spleen. Red color shades indicate higher and green shades indicate lower mRNA levels as compared with the respective mRNA levels in spleen. For example, note that mouse kidney (relative to mouse spleen) expresses much higher mRNA levels for most of the inflammasome-related genes as compared with human kidney (relative to human spleen).

THE ROLES OF INFLAMMASOMES IN KIDNEY DISEASE

Inflammasomes and the Biology of Chronic Kidney Disease

The inflammasome likely plays a role in chronic kidney disease. Inflammasome-regulated cytokines such as IL-1β and IL-18 are implicated in animal models or human forms of chronic kidney disease (Table 3). First, IL-1β and IL-18 induce mesenchymal markers in tubular epithelial cells in a dose-dependent manner.67,68 In humans, IL-18 and caspase-1 are expressed in renal tubular epithelium and patients with chronic kidney disease or the nephrotic syndrome exhibit elevated levels of IL-18.69–72 Similarly, IL-18 neutralization prevents renal injury and fibrosis after unilateral ureteric obstruction (UUO) in mice.73

Renal tubular cell injury occurs as a result of various insults, including ischemia, obstruction, and immune-mediated mechanisms that result in the release of endogenous cellular components capable of...
activating the NLRP3 inflammasome.54 Many DAMPs released during renal injury are capable of activating the NLRP3 inflammasome, including reactive oxygen species, extracellular ATP, uric acid, nucleic acids, and extracellular matrix components such as hyaluronic and biglycan.28,35,56,74–76 This premise has been confirmed in studies using the UUO model of chronic progressive kidney disease in mice.77 ATP in the mitochondrial fraction of necrotic cells activates the NLRP3 inflammasome through P2X<sub>7</sub> receptors.25,63,74 Consistent with these data, P2X<sub>7</sub>−/− mice exhibit less tubular injury and reduced inflammation and fibrosis after UUO compared with wild-type mice.78

In addition to ATP, other cellular factors also activate the NLRP3 inflammasome and play a role in chronic kidney disease, including the extracellular matrix components biglycan, hyaluronan.75,76 In the case of biglycan, mice deficient in this extracellular matrix protein are resistant to injury after UUO.76 Recent studies from our group confirm a role for the NLRP3 inflammasome in chronic kidney disease. Markers of inflammasome activation (including IL-1β, IL-18, and caspase-1 processing) are increased over a 14-day time course in mice after UUO. Compared with wild-type controls, NLRP3<sup>−/−</sup> mice exhibit a reduction in tubular injury and inflammation in this model.79 Furthermore, in a cohort of renal biopsies from patients with nondiabetic kidney disease, levels of mRNA encoding NLRP3 correlate with renal function, strongly suggesting that NLRP3 contributes to the pathogenesis of chronic kidney disease.79

### Table 3. Renal disease phenotype of knockout versus wild-type mice

<table>
<thead>
<tr>
<th>Model</th>
<th>IL-1R&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>IL-1β&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>Caspase 1&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>NLRP3&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>ASC&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>P2X&lt;sub&gt;7&lt;/sub&gt;&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>IL-1Ra</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgAN (dby)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury (postischemic)</td>
<td>?</td>
<td>?</td>
<td>127</td>
<td>63</td>
<td>63</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis (UUO)</td>
<td>?</td>
<td>?</td>
<td>73</td>
<td>?</td>
<td>79</td>
<td>78</td>
<td>128</td>
</tr>
</tbody>
</table>

IC-GN, immune complex glomerulonephritis; aNSN, autologous nephrotoxic serum nephritis; MRL/lpr, mouse MRL lymphoproliferation strain; BSA, bovine serum albumin-induced glomerulonephritis; ?, unknown; IgAN, IgA nephropathy; postischemic, ischemia-reperfusion injury.

### Inflammasomes and the Biology of Acute Kidney Injury

Acute tubular necrosis (ATN) is the most common cause of acute renal injury. Acute tubular injury that results in ATN can be induced by nonmicrobial stimuli such as ischemia-reperfusion during hypotension/shock and toxins such as drugs or radiographic contrast. ATN is associated with an inflammatory response that includes monocyte/macrophage and neutrophil recruitment to the kidney, which is detrimental and worsens renal injury.80,81 The data supporting the role of the inflammasome in acute kidney disease are strong. Numerous studies in humans and animal models of acute renal disease show elevated levels of IL-1β and/or IL-18. These models include ischemia/reperfusion injury, toxin-induced (cisplatin) tubular injury in rodents,82–85 and in urine bioprofiles of critically ill patients with ATN.86 The role of the inflammasome in acute renal failure is further strengthened by the finding that caspase-1-deficient mice are more resistant to various types of acute tubular injury, including cisplatin and ischemia-induced acute renal failure.82,84 Recently, Iyer and colleagues83 confirmed a role for the NLRP3 inflammasome and ASC in acute ischemia/reperfusion kidney injury in mice. The activation of the NLRP3 inflammasome by necrotic cells is secondary to the extracellular matrix components biglycan and hyaluronan and mitochondrial ATP acting through P2X<sub>7</sub> receptors.

### Future Perspective and Directions for Research

The NLRs and the inflammasomes are emerging as mediators of microbial and nonmicrobial diseases. Acute and chronic kidney disease involve the release and generation of factors such as reactive oxygen species, ATP, uric acid, and cholesterol crystals that correlate with disease severity and also activate these pathways. Future studies need to address the potential role of NLR and inflammasome signaling in renal cells and in animal disease models. Respective knockout mice for many inflammasome-related proteins are available for this purpose. Studies using human renal biopsies will be useful to determine the spatial and temporal expression of inflammasome components inside of the kidney and to correlate these findings with disease activity or prognosis. Gene polymorphism studies on suitable patient cohorts could help to determine the functional significance of human expression data. Finally, IL-1R antagonist or anti-IL-1 antibodies are approved drugs that might be tested, off-label, for their potential to modulate kidney disease, which would represent the ultimate proof of significance of the inflammasome-caspase-1/IL-1β/18 axis in kidney disease. This approach may not only offer a potentially fruitful area of research, but it will also hopefully lead to novel and specific therapies for patients with kidney disease.

In conclusion, NLRs and inflammasomes form a unique class of pattern recognition molecules that integrate multiple bacterial, viral, and endogenous danger signals into the immediate secretion of IL-1β and IL-18. As such, inflammasomes represent proximal and complementary elements of innate immune activation because subsequent IL-1R signaling
drives the same myeloid differentiation primary response gene (88)-dependent signaling pathway as the TLRs. Evolving data suggest that the inflammasome-caspase-1–IL-1β axis contributes to acute and chronic inflammation and tissue remodeling in the kidney. IL-1R antagonist and anti-IL-1 antibodies are used to validate the functional role of IL-1 in human disease. The time has come for the field of nephrology to characterize the expression and functional roles of inflammasome-related immune activation in animal models and human samples to specifically define which human kidney diseases qualify for the therapeutic blockade of this innate immune pathway.

DISCLOSURES

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